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SPECIAL ARTICLE

Role of Tranexamic Acid in Obstetrics and Gynecology

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ABSTRACT

Tranexamic acid is a synthetic lysine derivative that exerts an antifibrinolytic effect by reversibly blocking the lysine binding sites on plasminogen, thus preventing fibrin degradation. It has been approved by Food and Drug Administration for treatment of heavy menstrual bleeding and short-term prevention in patients with hemophilia. However, the role of tranexamic acid in obstetrics and gynecology is promising. This review aims to explore the role of tranexamic acid in obstetrics and gynecology.

Keywords: tranexamic acid, obstetrics, gynecology, postpartum hemorrhage, menorrhagia.

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Tranexamic acid

Tranexamic acid is a synthetic lysine derivative that exerts an antifibrinolytic effect by reversibly blocking the lysine binding sites on plasminogen, thus preventing plasmin (which is still formed by activation of plasminogen by a plasminogen activator) from interacting with lysine residues on the fibrin polymer and subsequent fibrin degradation[1].

The bioavailability of tranexamic acid was significantly higher after intravenous (IV) and intramuscular (IM) administration compared to oral administration. The bioavailability after IV, IM, and oral administration were 100%, 76.7%, and 36.4%, respectively. The time to peak concentration was also significantly shorter for IV administration compared to IM and oral administration[2].

The pharmacokinetics of tranexamic acid are not affected by the presence of food in the gastrointestinal tract; the oral bioavailability is approximately 34%. After oral administration of a single dose of 2 g to 10 fasting healthy male volunteers, the mean maximum plasma concentration of tranexamic acid was 14.4 mg/L and was achieved 2.8 hours postdose. The area under the concentration time curve from 0–6 hours was 59.5 mg*h/L. Tranexamic acid is minimally bound to plasma proteins (about 3%) at therapeutic plasma concentrations (5–10 mg/L), and this appears to be fully accounted

for by binding to plasminogen[1].

The main route of elimination of tranexamic acid is through the kidneys. After oral administration of 250 or 500 mg of tranexamic acid to healthy adults, 40 - 70% of the administered dose was excreted unchanged in the urine within 24 hours. The terminal elimination half-life is about 2 hours[1].

Dosage and administration

Tranexamic acid is approved for the treatment of menorrhagia (blood loss of > 80mL per cycle). The organic pathology as the cause of heavy menstrual bleeding should be excluded before initiating treatment. The drug is available for oral administration as 250 mg or 500 mg tablets and/or capsules and as a syrup containing 500 mg in 5 ml[1].

The recommended dosage of tranexamic acid differs from region to region. The recommended oral dose for the treatment of patients with menorrhagia is 1 to 1.5 g, 3-4 times daily for 3 to 4 days. The total daily oral dose should not exceed 4 g and treatment should be started once heavy menstrual bleeding has started[1].

Indication

Abnormal bleeding and its symptoms in hemorrhagic disease (purpura, aplastic anemia, cancer, leukemia, etc.), bloody sputum and hemoptysis in pulmonary tuberculosis, renal bleeding, genital bleeding, bleeding in prostatomegaly, abnormal bleeding during operation; menorrhagia[3].

The only Food and Drug Administration-approved usage of tranexamic acid is for heavy menstrual bleeding and short-term prevention in patients with hemophilia. This includes tooth extractions in patients with hemophilia, as well as menorrhagia in these patients[4, 5].

Contraindications and side effects

Tranexamic acid is generally well tolerated. It does not interfere with other coagulation factors; therefore, the risk of venous thromboembolism is not increased in those treated with the drug. The most common side effects are gastrointestinal complaints, such as nausea, vomiting, or diarrhea[6]. Another frequently experienced symptom is dysmenorrhea[6].

Tranexamic acid is contraindicated in women with active thromboembolic disease or a history or intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion[7]. Casati et al reported that although the prevalence of postoperative complications in patients undergoing elective cardiac surgery did not increased in those receiving infusion of tranexamic acid infusion, an increased risk of procoagulant response due to antifibrinolytic treatment also was observed[8].

Due to the antifibrinolytic effect of tranexamic acid, its use can decrease bleeding. Therefore, it may play a role in obstetrics and gynecology. Here is an overview of its role in obstetrics and gynecology:

Role of tranexamic acid in obstetrics

1. Treatment of postpartum hemorrhage (PPH)

Tranexamic acid has been used as an additional treatment for PPH due to the related morbidity and mortality. More than 20,000 patients with PPH were arbitrarily grouped to receive tranexamic acid or a placebo in the WOMAN trial. Although there was no discernible change in thrombosis rates, the death rate from bleeding was much lower in the tranexamic acid group (1.5% vs 1.9%, p = 0.045), especially in women given treatment within 3 hours of giving birth (1.2% in the tranexamic acid group vs 1.7% in the placebo group, p = 0.008). However, hysterectomy was not reduced with tranexamic acid (3.6% of patients in the tranexamic acid group versus 3.5% in the placebo group, p = 0.84)[9].

The American College of Obstetricians and Gynecologists (ACOG) 2017 recommended that tranexamic acid should be considered in the setting of obstetric hemorrhage when initial medical therapy fails due to mortality reduction findings[10].

2. Prevention of PPH

Many studies have evaluated tranexamic acid

in prevention of PPH, either low-risk or high-risk patients. In low-risk patients, a study demonstrated that among women who underwent cesarean delivery and received prophylactic uterotonic agents, tranexamic acid treatment resulted in a significantly lower incidence of calculated estimated blood loss greater than 1000 ml or red blood cell transfusion on day 2 than placebo, but it did not result in a lower incidence of hemorrhage-related secondary clinical outcomes[11].

Ogunkua et al conducted a study to evaluate if prophylactic tranexamic acid treatment reduces calculated blood loss when compared to placebo in women undergoing an elective repeat cesarean delivery. They found that prophylactic treatment with tranexamic acid did not decrease the mean calculated blood loss. Significantly fewer participants had calculated blood loss > 2000 mL in the tranexamic acid group than in the placebo group and had lower D-dimer levels at 24 hours[12].

One meta-analysis suggested that prophylactic tranexamic acid administration is effective among women undergoing cesarean delivery in lowering postpartum blood loss and limiting hemoglobin drop[13].

For a high risk of PPH, Neumann et al conducted a study to assess the role of tranexamic acid in reducing blood loss during elective and unscheduled cesarean deliveries in women at high risk of postpartum hemorrhage. High risk factors for postpartum hemorrhage included obesity, hypertension, multiparity, previous cesarean delivery, multiple pregnancy, abnormally implanted placenta, placenta previa, abruption, uterine leiomyomas, polyhydramnios, and fetal macrosomia. Women at high risk of postpartum hemorrhage undergoing cesarean delivery were recruited and randomized to receive tranexamic acid (500 mg intravenously) or placebo (1:1) at least 10 minutes before the skin incision. A total of 212 women met the inclusion criteria and were randomized (tranexamic acid (n = 106) and placebo (n = 106)). They found that high risk women who received tranexamic acid had significantly less blood loss than women who received placebo. Mean blood loss estimates were 400.9 ml in the tranexamic acid group and 597.9 mL in the placebo group ($p < 0.001$). No woman was transfused in either group[14].

Ortuanya et al evaluated the effectiveness and safety of tranexamic acid in reducing intraoperative blood loss when administered prior to cesarean delivery in women at high risk of postpartum bleeding. Intravenous 1 g of tranexamic acid or placebo was used in a 1:1 ratio. They found that the tranexamic acid group compared to the placebo group showed significantly lower mean blood loss (442.94 ± 200.97 versus 801.28 ± 258.68 mL, $p = 0.001$), higher mean postoperative hemoglobin (10.39 ± 0.96 versus 9.67 ± 0.86 g/dL, $p = 0.001$), lower incidence of postpartum hemorrhage (1.0% versus 19.0%, $p = 0.001$) and lower need for use of additional uterotonic agents after routine management of the third stage of labor (39.0% versus 68.0%, $p = 0.001$), respectively[15].

Sentilhes et al compared the effect of tranexamic acid vs placebo to prevent blood loss after cesarean delivery among women with multiple pregnancies. Women with cesarean delivery before or during labor at 34 weeks of gestation were randomized to receive 1 g of tranexamic acid (n = 160) or placebo (n = 159), both with prophylactic uterotonics. They found that among women with multiple pregnancy and cesarean delivery, prophylactic tranexamic acid did not reduce the incidence of any blood loss-related outcomes[16].

From the evidence above, the ACOG states that current data are insufficient to recommend tranexamic acid prophylaxis for postpartum hemorrhage outside of the context of research[10, 12].

Role of tranexamic acid in gynecology

Tranexamic acid also plays a role in gynecology. Here is an overview of its role in gynecology.

1. Heavy menstrual bleeding

Tranexamic acid has been evaluated in the treatment of heavy menstrual bleeding. There has been a study that aimed to evaluate the effectiveness

of oral tranexamic acid treatment in patients with excessive dysfunctional perimenopausal menorrhagia. All patients (n = 132) took 500 mg of tranexamic acid (Transamine® 3 capsule 2 times per day) during their menstruations. They concluded that oral tranexamic acid is a reasonable treatment option for patients with excessive dysfunctional perimenopousal bleeding with a response rate[17].

2. Myoma uteri

- Myomectomy

A study aimed aim to compare the efficacy and safety profile versus tranexamic acid with ethamsylate to reduce bleeding during myomectomy. They found that oxytocin and tranexamic acid with ethamsylate had no significant value in lowering intraoperative blood loss compared to placebo for abdominal myomectomy which opens a new question about the role of hemostatic drug during myomectomy especially in centers with limited resources and had higher rates[18].

- Bleeding from myoma uteri

A pivotal randomized control trial investigating the effects of tranexamic acid on heavy menstrual bleeding found that tranexamic acid significantly reduced heavy menstrual bleeding; however, the study did not characterize leiomyomas[19]. The presence of leiomyomas was not considered an abnormal finding unless the leiomyomas were of sufficient number and size to warrant surgical management. In this multicenter, double-blind, parallel group study, women with heavy menstrual bleeding were randomized to receive tranexamic acid (1.3 g per dose) or placebo. The study found that women who received tranexamic acid (n=115) met all three primary efficacy end points: first, a significantly greater reduction in menstrual blood loss of -69.6 mL (40.4%) compared with -12.6 mL (8.2%) in the 72 women who received placebo (P<0.001); reduction of menstrual blood loss exceeding a prespecified 50 mL; and last, reduction of menstrual blood loss considered meaningful to women[19]. Tranexamic acid does not treat the fibroid directly, nor does there exist long-term treatment data[20].

3. Irregular uterine bleeding from contraception

There have been several studies to evaluate the treatment of tranexamic acid in irregular uterine bleeding from contraception. A randomized, double-blind study in women with irregular uterine bleeding from IM depot medroxyprogesterone acetate use found that a significantly higher proportion of women treated with tranexamic acid (250 mg 4 times daily for 5 days) (n = 50) compared to placebo (n = 49) stopped bleeding within 7 days after starting therapy (88% vs 8.2%, $p < 0.001$). At 4 weeks after treatment, a bleeding-free interval of > 20 days was found in 68% of subjects treated with tranexamic acid and 0% treated with placebo($p < 0.001$)[21].

Another study in women with irregular uterine bleeding secondary to levonorgestrel implants (Norplant®), found that bleeding stopped within 1 week in a significantly higher proportion of women treated with tranexamic acid (500 mg 4 times daily for 5 days) (n = 34) than with placebo (n = 34) (64.7% vs 35.3%, $p = 0.015$). However, 4 weeks after treatment, there were no significant difference between the tranexamic acid and placebo groups in the proportion of patients who had stopped bleeding (58.8 vs 76.5%) or in the mean duration of bleeding or spotting days (15.4 vs 12.7 days)[22].

From these studies, tranexamic acid may have a benefit in short-term treatment of irregular uterine bleeding from contraception.

4. Gynecological surgery

There have been a few studies to evaluate tranexamic acid for reducing blood loss in gynecological surgeries[23-26]. One study found that a single dose of intravenous tranexamic acid given 15 minutes before surgery could significantly reduce measurement blood loss in surgical staging for endometrial cancer[23]. Another study found that high-dose tranexamic acid was more effective in reducing

blood loss and blood transfusion without increasing the risk of postoperative complications. But the low dose was not effective[24]. Bahadori et al found that prophylactic administration of tranexamic acid resulted in a significant reduction in need for blood transfusion and the duration of hysterectomy[25]. Topsoee et al found that prophylactic treatment with tranexamic acid reduced the overall total blood loss in benign hysterectomy[26]. However, due to the limited number of studies, the clinical use of tranexamic acid for reducing blood loss in gynecological surgeries needs further investigations.

Conclusion

In conclusion, tranexamic acid plays a vital role in obstetrics and gynecology. It is effective in treating postpartum hemorrhage and heavy menstrual bleeding. For other indications, such as prevention of postpartum hemorrhage, heavy bleeding from myoma uteri, irregular bleeding from contraception, and reducing blood loss in gynecological surgeries, further research is still needed.

Potential conflicts of interest

The author declares no conflicts of interest.

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